Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 05/01/2022**
Policy Number: PA.CP.PHAR.319	**Effective Date: 01/2018** **Revision Date: 04/2022**
Policy Name: Ipilimumab (Yervoy)	

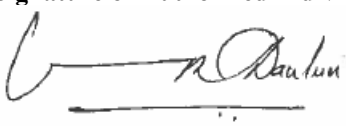
Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL -** *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

2Q 2022 annual review: revisions made per NCCN – for melanoma, added pathway for use as a single agent or in combination with Keytruda or Imlygic; for HCC, added additional optional for prior use of Tecentriq + bevacizumab; for NSCLC, removed use in disease positive for tumor mutation burden biomarker, revised requirement for "progression on PD-1/PD-L1 inhibitors" to "no contraindications to PD-1/PD-L1 inhibitors", clarified criteria regarding disease mutation status (unknown status is no longer allowed, and prior targeted therapy is now only required for ROS1 and EGFR S768I, L861Q, and/or G719X mutations), and removed requirement for PD-L1 ≥ 1% as it is not necessary given allowable compendial uses; for uveal melanoma, added requirement that disease is metastatic; updated Appendix D to reflect NCCN's stance on SCLC and TMB NSCLC; references reviewed and updated.

Name of Authorized Individual (Please type or print): **Venkateswara R. Davuluri, MD**	**Signature of Authorized Individual:** 

Clinical Policy: Ipilimumab (Yervoy)

Reference Number: PA.CP.PHAR.319
Effective Date: 01/2018
Last Review Date: 04/2022

Coding Implications
Revision Log

Description
Ipilimumab (Yervoy®) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody.

FDA Approved Indication(s)
Yervoy is indicated for:

- **Melanoma**
  - Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older)
  - Treatment of adult patients with unresectable or metastatic melanoma, in combination with nivolumab
  - Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
- **Renal cell carcinoma (RCC)**
  - Treatment of patients with intermediate or poor risk, previously untreated advanced RCC, in combination with nivolumab
- **Colorectal cancer (CRC)**
  - Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab*
- **Hepatocellular carcinoma (HCC)**
  - In combination with nivolumab, the treatment of patients with HCC who have been previously treated with sorafenib*
- **Non-small cell lung cancer (NSCLC)**
  - In combination with nivolumab, for the first-line treatment of adult patients with metastatic NSCLC whose tumors express programmed death-ligand 1 (PD-L1) ≥ 1% as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations
  - In combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations
- **Malignant pleural mesothelioma**
  - Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Pennsylvania Health and Wellness ® that Yervoy is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all):

1. Diagnosis of unresectable, metastatic, lymph node positive, or recurrent melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Prescribed in one of the following ways (a or b):
   a. As a single agent;
   b. In combination with Opdivo®, Keytruda®, or Imlygic®,* and both of the following (i and ii):
      i. Member has unresectable or metastatic melanoma;
      ii. Age ≥ 18 years;
      **Prior authorization may be required for Opdivo, Keytruda, and Imlygic*
5. Request meets one of the following (a, b, or c):*
   a. Unresectable or metastatic disease: Dose does not exceed 3 mg per kg every 3 weeks for a maximum of 4 doses;
   b. Adjuvant treatment: Dose does not exceed 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 6 months

B. Renal Cell Carcinoma (must meet all):

1. Diagnosis of advanced or metastatic renal cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Prescribed in combination with Opdivo®;
   **Prior authorization may be required for Opdivo*
5. Request meets one of the following (a or b):
   a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 16 weeks (maximum of 4 doses)

C. Colorectal Cancer (must meet all)**:**

1. Diagnosis of MSI-H or dMMR colorectal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Disease is advanced, progressive, unresectable or metastatic;
5. Prescribed in combination with Opdivo;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;

b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 16 weeks (maximum of 4 doses)

D. Hepatocellular Cancer (HCC) (must meet all)**:**
1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Member has previously received Nexavar®, Lenvima®, Tecentriq® + bevacizumab (*Mvasi® and Zirabev™ are preferred*), or Imfinzi®;
   **Prior authorization may be required for Nexavar, Lenvima, Tecentriq, bevacizumab, and Imfinzi*
5. Prescribed in combination with nivolumab (Opdivo);
   **Prior authorization may be required for Opdivo*
6. Documentation of Child-Pugh Class A status;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 3 mg/kg IV every 3 weeks for a maximum of 4 doses;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 16 weeks (maximum of 4 doses)

E. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of recurrent, advanced or metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Opdivo;
   **Prior authorization may be required for Opdivo*
5. Member does not have contraindication to PD-1/PD-L1 inhibitor therapy (e.g., Opdivo, Keytruda, Tecentriq, Imfinzi) (*see Appendix D*);
6. Request meets one of the following (a, b, c, or d):*
   a. Disease mutation status is negative for actionable biomarkers (EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET), and member has not received prior systemic therapy for advanced disease;
   b. Disease mutation status is positive for EGFR S768I, L861Q, and/or G719X, and member has received prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib;
   c. Disease mutation status is positive for ROS1 rearrangement, and member has received prior crizotinib, entrectinib, or ceritinib;
   d. Disease mutation status is positive for EGFR exon 20, KRAS G12C, NRTK1/2/3, BRAF V600E, MET exon 14 skipping, or RET rearrangement;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration: 6 months

F. Malignant Pleural Mesothelioma (must meet all)**:**

1. Diagnosis of unresectable malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Opdivo;*
   **Prior authorization may be required for Opdivo.*
5. Request meets one of the following (a or b):
   a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

G. NCCN Compendium Indications (off-label) (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. MSI-H or dMMR small bowel adenocarcinoma;
   b. Metastatic uveal melanoma;
   c. Other NCCN recommendations listed as category 1, 2A, or 2B;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. For MSI-H/dMMR small bowel adenocarcinoma: Prescribed in combination with Opdivo;*
5. For uveal melanoma: Prescribed as a single agent or in combination with Opdivo;*
   **Prior authorization may be required for Opdivo.*
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

H. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. Melanoma-Unresectable or Metastatic

1. Reauthorization beyond 16 weeks is not permitted. Members will need to be re-evaluated against the initial approval criteria, at a minimum of 3 months since initial treatment discontinuation.
   a. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
   b. Member is responding positively to therapy.

B. Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma (must meet all):

1. Reauthorization beyond 16 weeks is not permitted. Members will need to be re-evaluated against the initial approval criteria.

a. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
b. Member is responding positively to therapy.

C. Melanoma (Adjuvant Treatment), Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma (must meet all):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, or c):
   a. For melanoma: New dose does not exceed 10 mg/kg per dose;
   b. For NSCLC and malignant pleural mesothelioma: New dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 12 months or up to a total duration of 3 years (cutaneous melanoma) or 2 years (NSCLC, malignant pleural mesothelioma), whichever is less

D. NCCN Compendium Indications (off-label) (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

E. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to PA.CP.PMN.53

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
ALK: anaplastic lymphoma kinase
BRAF: B-Raf proto-oncogene, serine/ threonine kinase
CRC: colorectal cancer
CTLA-4: cytotoxic T-lymphocyte antigen 4
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration

HCC: hepatocellular carcinoma
MET: mesenchymal-epithelial transition
MSI-H: microsatellite instability-high
PD-1: programmed death-1
PD-L1: programmed death-ligand 1
RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Opdivo® (nivolumab)	**MSI-H/dMMR small bowel adenocarcinoma** 3 mg/kg IV once every 3 weeks for four doses, then 3 mg/kg IV or 240 mg IV every 2 weeks with or without ipilimumab	RCC, HCC: 480 mg/dose CRC, small bowel adenocarcinoma: 240 mg/dose
Nexavar (sorafenib)	**HCC** 400 mg PO BID	800 mg/day
Lenvima (lenvatinib)	**HCC** 12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients < 60 kg)	12 mg/day
Tecentriq (atezolizumab) + bevacizumab (Avastin®, Mvasi, Zirabev)	**HCC** Tecentriq: 840 mg IV every 2 weeks, 1,200 mg IV every 3 weeks, or 1,680 mg IV every 4 weeks Bevacizumab: 15 mg/kg IV every 3 weeks	See regimen
platinum-containing regimens	**NSCLC – squamous cell carcinoma** paclitaxel + carboplatin dose varies **NSCLC – nonsquamous cell carcinoma** pemetrexed + [carboplatin or cisplatin] dose varies	Varies
EGFR S768I, L861Q, and/or G719X targeted therapies: afatinib, osimertinib, erlotinib,	**NSCLC** Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
gefitinib, dacomitinib		
ROS1 targeted therapies: crizotinib, entrectinib, ceritinib	**NSCLC** Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications and Boxed Warnings

- Bristol-Myers Squibb was released from the REMS program for Yervoy in March 2015.
- Boxed warning(s): none reported
- Contraindiation(s): none reported

Appendix D: General Information

- NCCN no longer recommends the use of Yervoy for small cell lung cancer or tumor mutation burden NSCLC.
- Per NCCN, contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (i.e., EGFR exon 19 deletion or L858R, ALK rearrangements), which would predict lack of benefit.

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma (adjuvant treatment)	10 mg/kg IV every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity.	10 mg/kg/dose
Melanoma (unresectable or metastatic)	3 mg/kg IV every 3 weeks for a total of 4 doses	3 mg/kg/dose
RCC	Nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	1 mg/kg/dose
CRC	Nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses or until intolerable toxicity or disease progression, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	1 mg/kg/dose
HCC	Nivolumab 1 mg/kg IV, followed by ipilimumab 3 mg/kg IV on the same day, every 3 weeks for a	3 mg/kg/dose

Indication	Dosing Regimen	Maximum Dose
	maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	
NSCLC	In combination with nivolumab: nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression In combination with nivolumab and platinum-doublet chemotherapy: nivolumab 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression	1 mg/kg/dose
Malignant pleural mesothelioma	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.	1 mg/kg/dose

V. Product Availability

Single-use vials: 50 mg/10 mL, 200 mg/40 mL

VI. References

1. Yervoy Prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; November 2020. Available at: https://packageinserts.bms.com/pi/pi_yervoy.pdf. Accessed January 28, 2022.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed January 28, 2022.
3. National Comprehensive Cancer Network. Malignant Pleural Mesothelioma Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed January 28, 2022.
4. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed January 28, 2022.
5. Hellman MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med. 2019 November; 381(21):2020-2031.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9228	Injection, ipilimumab, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Criteria added for new FDA indication: advanced renal cell carcinoma in combination with nivolumab; removed malignant pleural mesothelioma due to NCCN 2B recommendation status; added oncologist specialist requirement for all covered indications; summarized NCCN and FDA-approved uses for improved clarity; added up to a total tx duration of 3 years for cutaneous melanoma per PI; added failure of platinum-containing chemotx for SCLC per NCCN; allowed continuity of care for continued approval; clarified continued therapy language for unresectable or metastatic melanoma that reauthorization beyond 16 weeks is not permitted from reauthorization is not permitted; references reviewed and updated.	05/2018	
2Q 2019 annual review: criteria added for colorectal cancer in combination with nivolumab; added coverage for malignant pleural mesothelioma; references reviewed and updated.	04/2019	
2Q 2020 annual review: criteria added for hepatocellular carcinoma (HCC) in combination with nivolumab; added NCCN compendium-supported indications of small bowel adenocarcinoma, uveal melanoma, non-small cell lung cancer; condensed NCCN compendium-supported indications into one subsection; references reviewed and updated.	04/2020	
FDA approved malignant pleural mesothelioma added. Ad hoc changes: melanoma unresectable/metastatic disease and lymph node positive disease criteria sets combined; for HCC, Lenvima added as a prior therapy option per NCCN; for NSCLC, single agent therapy for TMB positive tumor added and combination therapy for RET rearrangement added per NCCN, combination therapy changed from Yervoy and platinum doublet therapy to Yervoy plus/minus a platinum based regimen to accommodate NCCN recommended uses; references reviewed and updated.	01/2021	
2Q 2021 annual review: clarified RCC as “advanced or metastatic” per NCCN and prescribing information, removed SCLC from off-label indications as this is no longer supported by NCCN, and removed boxed warning from Appendix C per prescribing information; references reviewed and updated.	04/2021	
2Q 2022 annual review: revisions made per NCCN – for melanoma, added pathway for use as a single agent or in combination with	04/2022	

Reviews, Revisions, and Approvals	Date	Approval Date
Keytruda or Imlygic; for HCC, added additional optional for prior use of Tecentriq + bevacizumab; for NSCLC, removed use in disease positive for tumor mutation burden biomarker, revised requirement for "progression on PD-1/PD-L1 inhibitors" to "no contraindications to PD-1/PD-L1 inhibitors", clarified criteria regarding disease mutation status (unknown status is no longer allowed, and prior targeted therapy is now only required for ROS1 and EGFR S768I, L861Q, and/or G719X mutations), and removed requirement for PD-L1 ≥ 1% as it is not necessary given allowable compendial uses; for uveal melanoma, added requirement that disease is metastatic; updated Appendix D to reflect NCCN's stance on SCLC and TMB NSCLC; references reviewed and updated.		